

Durability of Response in Children Treated with Pegylated Interferon
alfa-2a +/- Ribavirin for Chronic Hepatitis C

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ABSTRACT

Objectives: No long-term data have been published on the durability of response following pegylated interferon (PegIFN) treatment in children with chronic hepatitis C (CHC). This prospective, multi-center, long-term follow-up (LTFU) study aimed to assess long-term durability of sustained virological response (SVR), long-term safety and tolerability, and the association between *IL28B* genotype and treatment response, in children previously treated with PegIFN alfa-2a ± ribavirin (RBV) in the PEDS-C trial.

Methods: Ninety-three patients were assessed for enrollment and 38 enrolled in the study. Patients attended two study visits: 5 (mean 5.6; range 4.1 - 6.6) and 6 (6.6; 5.1 – 7.7) years after treatment cessation. Standardized medical history, physical examination and laboratory testing were done at these visits. Reminder telephone calls were conducted at 4 and 8 months after the initial visit.

Results: The LTFU cohort was representative of the original PEDS-C cohort as both baseline and treatment characteristics were comparable. Of the 38 participants, 21 achieved SVR (responders) during the PEDS-C trial and 17 had not (non-responders). All 21 responders maintained undetectable HCV RNA during the LTFU (4.4 - 7.0 years after achieving SVR) in contrast to the non-responders who demonstrated persistent viremia. *IL28B* CC genotype was associated with SVR (67%, vs. 30% in non-CC, $p=0.028$).

Conclusion: Long-term durability of SVR is excellent following PegIFN alfa-2a treatment in children with CHC; SVR is higher in those with *IL28B* CC vs non-CC.

Keywords: pediatric viral hepatitis; antiviral therapy; PEDS C study; long term follow up

What is known:

- There are ~5 million children in the world with chronic hepatitis C (CHC) viremia
- Current FDA-approved therapy for children with CHC is pegylated interferon with ribavirin
- Durability of viral response in children treated with non-pegylated interferon and ribavirin is ~98% at 5 years of follow up

What is new:

- Durability of viral response in children with HCV treated with pegylated interferon and ribavirin is ~100% at 4 – 7 years of follow up
- Viral response in children treated with pegylated interferon and ribavirin is higher in children with *IL28B* CC vs. those with non-CC

Abbreviations:

CHC	chronic hepatitis C
HCV	hepatitis C virus
LTFU	long-term follow up
LLOD	lower limit of detection
CI	confidence interval
PegIFN	pegylated interferon
RBV	ribavirin
SAE	serious adverse events
SNP	single nucleotide polymorphism
SVR	sustained virological response

INTRODUCTION

HCV infection is a significant global health burden, with an estimated prevalence of approximately 115 million people globally (1.6% of the world's population) [1]. Eleven million of these individuals are below 15 years of age, of whom 5 million are viremic [1]. Children in China, Pakistan, Nigeria, Egypt, India and Russia account for more than 50% of the total pediatric infections [1]. Pediatric HCV infection prevalence varies significantly by region, ranging from 0.05-0.36% in the United States and Europe to 1.8-5.8% in some developing countries [2]. A similar trend is observed in the ratio of the prevalence of HCV in children compared to adults, which varies from approximately 1:25 in high-income countries to 1:4 in middle-income countries, and as high as 1:2 in low-income countries [1]. While vertical (mother-to-infant) transmission is the major route of pediatric infection in developed countries, horizontal transmission (e.g. contaminated needles or blood transfusion products) is the major route in developing countries [2].

The PEDS-C study enrolled 114 children with chronic hepatitis C (CHC) into a clinical trial of pegylated interferon (PegIFN) alfa-2a (Pegasys®) plus ribavirin (RBV, Copegus®) or placebo from December 2004 to May 2006 and the last patient completed the two-year follow-up in February 2010 [3]. The sustained virological response (SVR) rate was 53% (n=29/55) in children treated with combination therapy and 20% (n=12/59) in those treated with PegIFN alfa-2a plus placebo (p<0.001). SVR was maintained in 100% of children that were followed up for 2 years after cessation of therapy. In addition, 28/59 patients treated with PegIFN alfa-2a plus placebo were HCV RNA positive at Week 24, deemed non-responders and received additional 'open-label' compassionate use PegIFN alfa-2a + RBV treatment for a further 48 weeks duration.

Eleven of these 28 patients (39%) ultimately achieved SVR, which was maintained in all patients 2 years after completing treatment.

Longer-term durability of response in children treated with PegIFN with or without RBV has not been reported to date. In adults, durability of SVR 5 years after completing PegIFN treatment has been observed to be >99% [4] and cirrhosis appears to be a risk factor for long-term relapse [5].

The only published report of long-term follow-up in children is following non-pegylated interferon treatment thrice weekly with RBV, where the Kaplan–Meier estimate for sustained response at 5 years was 98% (95% CI, 95-100%) [6].

In adults with genotype 1 infection, several independent genome-wide association studies (GWASs) reported single nucleotide polymorphisms (SNP's) near the *IL28B* (IFN- λ) locus to be predictive of treatment response [7, 8]. Although recently a few pediatric studies have explored the effect of *IL28B* polymorphism on SVR in children, its role as a predictor of durability of response to treatment is still undetermined [9].

The purpose of this study was to perform a long-term follow-up (LTFU), up to 7 years after cessation of therapy, of a group of children previously treated with PegIFN alfa-2a \pm RBV in the PEDS-C study, and assess the long-term durability of SVR, long-term safety and tolerability, and the association between *IL28B* polymorphism and treatment response.

METHODOLOGY

Study Population

Patients were eligible for inclusion if they completed treatment with PegIFN alfa-2a \pm RBV in the PEDS-C study. Patients were excluded if they received PegIFN alfa-2a \pm RBV after the initial study period, received other treatment that the investigator judged could affect growth

(e.g. growth hormone therapy), or experienced serious illnesses unrelated to PegIFN treatment requiring >72 hours hospitalization that may have a negative impact on growth.

Study Procedures

The Institutional Review Board at each site and the Clinical Trials and Survey Corporation approved the study protocol. Informed consent was obtained from all patients, who were subsequently seen at study entry, contacted by telephone 4 and 8 months later, and seen again 1 year after study entry. Clinical and laboratory information collected included: HCV RNA (TaqMan-2.0-EDTA-C Assay, LLOD 10 IU/ml), clinical chemistries and thyroid function tests, *IL28B* polymorphisms (SNPs at rs12979860, comparing genotype CC vs. CT/TT) [10], and health-related quality of life data.

Statistical Analyses

Descriptive statistics were used for all analyses with exploratory analyses performed as appropriate. All statistical tests were two-sided and used the conventional $p < 0.05$ level of significance, with χ^2 and independent t-test being used as appropriate. RNA values were log-transformed to improve interpretability. All analyses were performed using SAS software version 9.2.

RESULTS

Subject Characteristics

All 93 patients who had completed the 2-year follow up in the original PEDS-C study, from 8 participating sites, were considered for enrollment. Thirty-eight were available and willing to participate in the LTFU study. Of the 55 others: 26 were not contactable, 8 had moved from the area, 7 received PegIFN/RBV re-treatment and 14 either refused consent or could not participate for other reasons. The patient disposition in the original PEDS-C study and this LTFU study is shown in Figure 1.

The LTFU cohort was found to be representative of the original PEDS-C cohort, both in terms of baseline characteristics (e.g. HCV genotypes) and treatment received (see Table). Twenty-one (55%) subjects had received PegIFN alfa-2a + RBV whilst 17 (45%) received PegIFN alfa-2a + placebo treatment. Ten of the 17 subjects treated with PegIFN alfa-2a + placebo, received additional PegIFN alfa-2a + RBV treatment for 24-48 weeks duration, after study week 24 via the 'compassionate use' treatment arm.

Durability of SVR

HCV RNA levels remained undetectable in 100% of responders but remained high in all non-responders during LTFU. Mean ALT levels were significantly lower in responders compared to non-responders at all follow-up time points. For example at LTFU visit 1, mean ALT levels in responders were normal at 23 U/L [95%CI 19-27] while they were elevated in non-responders at 53 U/L [95%CI 32-75] ($p < 0.05$).

IL28B and SVR

IL28B CC genotype was associated with higher rate of SVR, compared to CT/TT genotype (67% vs. 30% respectively, $p = 0.028$) (Figure 2).

Safety Analyses

There were no patient deaths and only 1 serious adverse event (hospitalization for depression) was reported. This SAE occurred 6.5 years post-treatment and was deemed unrelated to study treatment. There were no clinically significant changes in any laboratory or vital sign parameters with the exception of the HCV RNA and ALT values discussed above.

Long-term growth outcomes have been previously reported [11], and overall no long-term effects on height were observed. The results of health-related quality of life questionnaires will be reported separately.

DISCUSSION

The major finding of this study is that SVR following PegIFN alfa-2a ± RBV therapy in children with CHC is durable in 100% of patients for 4.4 to 7.7 years after treatment cessation. *IL28B CC* genotype was also observed to be associated with a greater chance of an SVR ($p=0.028$), which is consistent with data from adult and recent pediatric studies with CHC. Furthermore, PegIFN alfa-2a also shows an excellent long-term safety profile in treatment of children with HCV, including absence of long-term effects on growth [11].

The significance of the above finding is that PegIFN alfa-2a is currently widely available to the considerable global population of children and adolescents with HCV. Indeed, it has been estimated that approximately 50,000 HCV-infected infants are born every year [12], a fact which is especially sobering given that at present there is no known way to prevent maternal-fetal transmission.

Although direct acting anti-viral agents currently hold great promise for highly effective interferon-free treatment regimens [13], none have yet been approved for use in children and there could be challenges to widespread availability to children, particularly in low-income countries where the prevalence and burden of HCV infection is greatest.

The main limitation of this study is the relatively small number of patients that participated in the long-term follow-up. This is not surprising given that the average age of enrollees in the original PEDS-C study was 11 years and the long-term follow-up lasted up to 7.7 years after cessation of therapy. This meant that many patients had moved away from home for higher education or employment and were simply not available for participation in the LTFU study. However, the fact that the baseline and treatment characteristics of the LTFU cohort did not differ from the PEDS-C cohort indicates that the smaller LTFU cohort is representative of the original larger

cohort. Given that the LTFU cohort is representative of the larger cohort, it is unlikely that the 100% long-term durability rates observed in the LTFU cohort would significantly differ if the entire PEDS-C cohort participated in the LTFU.

Overall, the PEDS-C LTFU data indicate that children who achieve SVR during treatment with PegIFN alfa-2a, with or without RBV, have a very high likelihood of long-term maintenance of that response. Given the ~5 million HCV-infected children in the world, the current lack of approved direct-acting antiviral interferon-free regimens in the pediatric population, as well as the potential limited access to interferon-free regimens in the developing countries where HCV prevalence is highest, it is reassuring to confirm that SVR achieved in children with CHC with the current standard of care will be maintained for many years.

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FIGURE LEGENDS

Fig. 1. Patient Disposition

*3/11 PEDS-C sites did not participate in the LTFU study

Fig. 2.. Association between IL28B polymorphism and SVR rates in: (A) two randomized study arms (ITT population), and (B) all treatment arms (compassionate use arm included). Upper 95% CI depicted

Figure 1

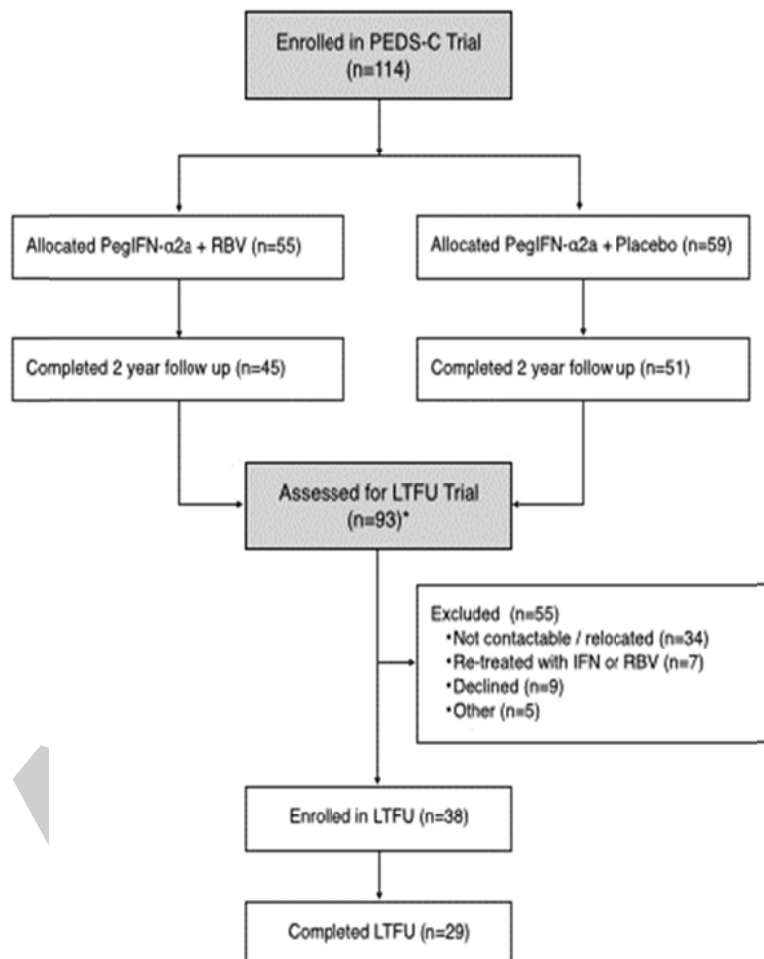


Figure 2

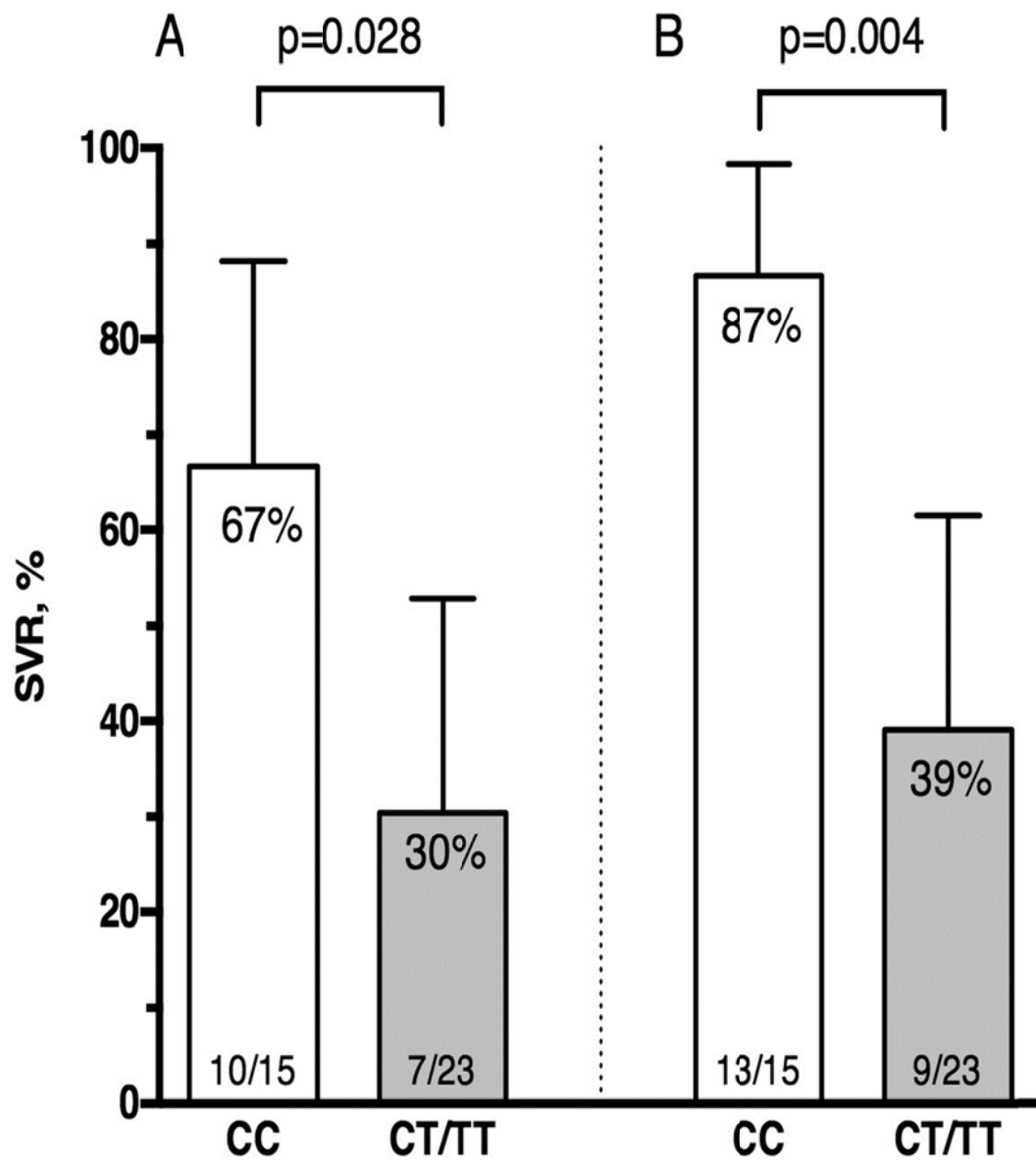


Table 1 Characteristics of PEDS-C and LTFU Cohorts

	PEDS-C	LTFU
	n=114	n=38
Demography, n (%)		
Male gender	63 (55)	23 (61)
Non-Caucasian race	23 (20)	7 (18)
Age (years), mean \pm SD	10.7 \pm 3.4	9.7 \pm 3.1
5-11 / 12-17 yrs.	60 (53) / 54 (47)	25 (66) / 13 (34)
BMI (kg/m ²), mean \pm SD	20.5 \pm 4.9	20.1 \pm 5.5
Baseline Characteristics, n (%)		
HCV Genotype 1 / 2 / 3 / 6	92 (81) / 7 (6) /	31 (81) / 1 (3) /
	13 (11) / 2 (2)	5 (13) / 1 (3)
Perinatal infection route	85 (75)	29 (76)
HCV RNA (Log IU/ML), mean \pm SD	6.24 \pm 0.83	6.12 \pm 0.92
ALT (U/L), mean \pm SD	54 \pm 36	51 \pm 29
Absent/minimal fibrosis (Ishak 0-2)	104/110 (95)	35/36 (95)
Treatment Characteristics, n (%)		
PegIFN alfa-2a + RBV	55 (48)	21 (55)
SVR	27/55 (49)	11/21 (52)
PegIFN alfa-2a + Placebo	59 (52)	17 (45)
SVR	12/59 (20)	6/17 (35)
Compassionate Use [‡]	28/59 (47)	10/17 (59)
SVR	11/28 (39)	5/10 (50)
Treatment duration, 24 / 48 / 76 wks	26 (23) / 76 (67)	5 (13) / 28 (74)
	/ 12 (10)	/ 5 (13)

[‡] PegIFN monotherapy non-responders were eligible for additional compassionate use combination therapy treatment